## *Remarks*

Upon entry of the foregoing amendment, claims 136, 137, 139-141, 143, 144 and 148-163 are pending in the application, with claims 136, 150 and 157 being the independent claims. Claims 136, 143 and 144 are sought to be amended. New claims 150-163 are sought to be added. Claims 142 and 145-147 are sought to be cancelled. Support for the amendment to claim 136 may be found, *e.g.*, in previous claim 142, page 7, paragraph [0017] of the specification as filed, Figure 11, and page 53, paragraph [0146] of the specification. Support for the amendments to claims 143 and 144 may be found, e.g., in prior claims 143 and 144. Support for new claim 150-156 may be found, *e.g.*, at pages 12-13, paragraph [0032], page 55, paragraph [0151], and throughout the specification. Support for new claims 157-163 may be found, *e.g.*, at page 55, paragraph [0151], pages 31-32, paragraph [0079] of the specification and throughout the specification.

Based on the above amendments and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

***Rejections under 35 U.S.C. § 112***

The Examiner rejected claims 136, 137, and 139-149 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner alleged that there is insufficient antecedent basis for "the polymerase binding site" in claim 136. The Examiner further alleged that it is unclear how the target molecule recited in the claim is detected using a template nucleic acid. Regarding claim 142, the Examiner alleged that it is unclear how

the template comprises a target molecule and a target site probe. The Examiner rejected claims 137, 139, and 140-149 based on their dependency on claim 136. Applicant respectfully traverses this rejection.

Solely to advance prosecution and not in acquiescence of the Examiner's rejection, Applicant has amended claim 136 and has deleted the phrase "wherein the RNA polymerase releases said oligonucleotide transcript without substantially translocating from the polymerase binding site" from the claim. Applicant has amended the preamble to recite a nucleic acid. In addition, Applicant has cancelled claim 142. Accordingly, Applicant respectfully believes that the rejections are now moot.

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

***Rejection under 35 U.S.C. § 102***

The Examiner has rejected claims 136, 137, 140, and 145-149 under 35 U.S.C. § 102(b) as allegedly anticipated by Sasaki *et al.* (*Proceed Nat Acad Sci USA*, 95:3455-3460 (1998)). The Examiner also rejected claims 136, 137, 139, 141-145, and 147-150 under 35 U.S.C. § 102(b) as allegedly anticipated by Daube *et al.* (*PNAS USA*, 91:9539-9543 (1994)("Daube *et al.*") as allegedly evidenced by Daube (Biochemistry, 33:340-347 (1994)). Applicant respectfully traverses these rejections.

Under 35 U.S.C. § 102, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

***1. Rejection over Sasaki et al.***

The Examiner contends that Sasaki *et al.*, as demonstrated by Figure 4 on p. 3457, teaches an abortive reiterative synthesis reaction wherein the abortive reaction is achieved by incorporation of four kinds of dye-3' dNTPs and detecting said oligonucleotide. See Office Action, p. 4.

Solely to advance prosecution and not in acquiescence of the Examiner's rejection, Applicant has amended claim 136 to specify that the nucleic acid template is incubated with a target site probe wherein the target site probe and nucleic acid form a bubble complex. Applicants respectfully note that the Examiner did not reject claim 142 as anticipated by Sasaki *et al.*, which recited a target site probe. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

Applicant has presented new claims directed to methods for detecting the presence of a target nucleic acid or protein in a biological or environmental sample utilizing abortive promoter cassettes. The crux of the Examiner's argument is that the limitation "abortive promoter cassette" is not specifically defined by the specification, and that the limitation encompasses any structure which comprises promoter sequence that is capable of effecting abortive reiterative synthesis. Applicant respectfully disagrees with the Examiner. Abortive promoter cassettes are described in the specification. The structures of the abortive promoter cassettes are recited in the claims. Applicant respectfully asserts that Sasaki *et al.* neither discloses, nor suggests methods for detecting the presence of a target nucleic acid or protein in a biological or environmental sample utilizing the abortive promoter cassettes as claimed.

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

*2. **Rejection over Daube et al.***

The Examiner asserts that Daube *et al.* disclose a method of detecting the presence of a target molecule from a plasmid, wherein the artisans conduct the step of ligating a transcriptional bubble complex to the target nucleic acid, followed by the generation of multiple abortive reiterative transcripts. Applicant respectfully traverses this rejection.

Solely to advance prosecution and not in acquiescence of the Examiner's rejection, Applicant has amended claim 136 to recite that the nucleic acid template is incubated with a target site probe wherein the target site probe and the nucleic acid of the biological or environmental sample form a bubble complex. Applicant respectfully asserts that Daube *et al.* do not teach incubation of a target nucleic acid with a single stranded target site probe wherein the nucleic acid and the target site probe form a bubble complex.

In addition, Applicant has presented new claims 157-163 directed to methods for detecting the presence of a target nucleic acid in a biological or environmental sample utilizing abortive promoter cassettes. In addition, the claims recite that the process is abortive and the transcript size is selected from the group consisting of 2 to about 26 nucleotides, about 26 to about 50 nucleotides and about 50 nucleotides to about 100 nucleotides in length. The structures of the abortive promoter cassettes are recited in the claims.

Applicant respectfully asserts that Daube *et al.* do not disclose an abortive reiterative process as claimed. Daube *et al.* describe transcription of a 226 bp runoff fragment and a 166 nucleotide product corresponding to RNA terminating at the T7Te

terminator. These products are the products of a processive transcription reaction and not the products of an abortive, reiterative process as claimed.

Daube *et al.* are solely interested in investigating the *mechanisms* of termination. Daube *et al.* describe ligating a construct to the oligonucleotide to investigate termination mechanisms. Daube *et al.* describe use of this complex *solely* as a tool to probe the properties of a functional elongation complex and termination mechanisms. In addition, Daube *et al.* does not provide any reason to use the bubble complex to detect a target nucleic acid in biological or environmental samples.

Daube *et al.* compared the termination efficiency of the bubble complex with a promoter driven template. Based on the results, Daube *et al.* teaches away from any expectation that transcription from the bubble complex is equivalent to transcription from a traditional promoter. Importantly, Daube *et al.* compared the termination efficiency of transcription from a promoter driven template and bubble complex and found that the termination efficiency of the bubble complex was very low (efficiency of 19%) compared with that of a promoter template (efficiency of 88%). *See* p. 9541 of Daube *et al.*. Daube *et al.* offers various possible theories for the low termination efficiency of bubble complex transcription and speculated that the lowered efficiency

> might reflect the tendency of the nascent RNA to rehybridize to the template DNA during *E.coli* RNA polymerase-catalyzed transcript elongation from the bubble duplex, since the resulting rehybridized transcript might be unable to form a termination hairpin (or other element of RNA secondary structure) required for intrinsic termination and RNA release.

*Id.* Daube *et al.* conducted experiments to further investigate the inefficiency of termination of transcripts generated from the bubble complex. The results of the

experiments ostensibly show that an RNA trap is necessary to improve efficiency to prevent reannealing of the nascent RNA to the non-complementary bubble sequence. Daube *et al.* hypothesized that the "residual level of termination obtained in the absence of an RNA trap can be attributed to the low level of RNA displacement that does occur under these conditions." *Id.* at 9542. Daube *et al.* further speculated about three possible mechanistic schemes, shown on p. 9542, to interpret the results. Daube *et al.* highlights the investigational nature of the complex by noting that "these complexes may also be useful in studying other regulatory aspects of transcript elongation and termination, such as pausing, attenuation, factor mediated anti-termination, and rho-dependent termination." *Id.* at 9542. Daube *et al.* also emphasize the need for additional comparative studies of promoter driven and bubble duplex transcription:

> [f]urther comparative studies with promoter bubble-less duplex constructs may prove useful in separating such promoter dependent effects from effects reflecting only the process of elongation.

*Id.* at p. 9543. Based on such description and characterization by Daube *et al.* of the complex, including differences of the complex in transcription termination *vis-a-vis* promoter-generated transcription termination, Applicant respectfully asserts that a person skilled in the art would not be motivated to use the abortive promoter cassette for diagnostic purposes to detect target nucleic acids in biological or environmental samples.

In addition, Applicant has presented new claims 150-156 directed to methods for detecting the presence of a protein in a biological or environmental sample utilizing abortive promoter cassettes. Applicant respectfully asserts that Daube *et al.* neither discloses or suggests attaching a protein to an abortive promoter cassette, and

synthesizing multiple copies of detectable oligonucleotide transcripts through abortive reiterative synthesis as claimed.

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

***Obviousness-type Double Patenting***

The Examiner rejected claims 136-147 for obviousness-type double patenting over various claims of the Applicant's issued patent and copending applications. Specifically, the Examiner rejected the Applicant's claims over the following: claims 1-34 of U.S. Patent No. 7,045,319; claims 26, 27, 103, 112, and 136-139 of copending Application No. 10/488,971; claims 1-22, 32-34 and 44 of copending Application No. 10/976,240; claims 11-27 of copending Application No. 10/425,037; and pending and/or elected claims of Application Nos. 10/602,045 and 10/607,136.

Applicant respectfully requests that the Examiner reconsider and withdraw these rejections, or hold the present rejections in abeyance, pending the identification of otherwise allowable subject matter, at which time Applicant will consider filing any necessary terminal disclaimers.

## *Conclusion*

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be

withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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